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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/675,927 | 09/29/2003 | Payman Amiri | 18773.004 | 2378 |

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| EXAMINER | |
|---|---|
| KANTAMNENI, SHOBHA | |
| **ART UNIT** | **PAPER NUMBER** |
| 1617 | |

| MAIL DATE | DELIVERY MODE |
|---|---|
| 09/30/2008 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/675,927 | AMIRI ET AL. | |
| | Examiner | Art Unit | |
| | Shobha Kantamneni | 1617 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *27 August 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *75-76,78,80,82-83,87-106,108-112* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *NONE* is/are allowed.

6)☒ Claim(s) *75,76,78,80,82,83,87-106 and 108-112* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Continued Examination Under 37 CFR 1.114*

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 08/27/2008 has been entered.

Applicant's amendment filed on 08/27/2008, wherein claims 75, 78, 82, 92, 93-94 have been amended, and new claim 112 has been added.

Upon further consideration, and in view of Applicant's amendment, the rejections made in the final office action are herein withdrawn.

Claims 75, 76, 78, 80, 82, 83, 87-106, 108-112 are pending, and examined herein.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 75-76, 78, 80, 82-83, 87-106, 108-112 are rejected under 35 U.S.C. 112, first paragraph, because the specification while being enabling for a method of inhibiting Raf kinase activity in a human or animal subject suffering from a Ras/mitogen-activated

protein kinase signal pathway-mediated cancer disorder selected from the group consisting of melanoma, breast cancer, prostate cancer, lung cancer, pancreatic cancer, thyroid cancer, bladder cancer, colon cancer, liver cancer, myeloid leukemia, and villous colon adenoma in a human or animal subject, comprising administering to the human or animal subject a composition comprising an amount of composition comprising specific compound represented by formula (I), does not reasonably provide enablement for inhibiting Raf kinase activity in a human or animal subject comprising administering a composition comprising **any compound** represented by formula (I) or ester or prodrug thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention without **undue experimentation**. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

> (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

**(1). The Nature of the Invention:**

All of the rejected claims are drawn to an invention which pertains to a method of inhibiting Raf kinase activity in a human or animal subject comprising administering a composition comprising compound represented by formula (I) or ester or prodrug thereof.

**(2). Breadth of the Claims:**

The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims. The claims encompass method of inhibiting Raf kinase activity in a human or animal subject comprising administering a composition comprising any compound encompassed by the formula illustrated by the broad structure of formula (I) or esters or prodrug thereof.

What's more, the scope of the compounds claimed to be useful for the treatment method is extremely broad.

**(3). Guidance of the Specification / (4). Working Examples:**

Applicant provides in the specification on pages 307-309 *in vitro* assay protocol, Raf Screening in general. The specification merely recites on page 309 "Using the procedures of Examples 1401 or 1402, the compounds of Examples 1-1094 were shown to have a raf kinase inhibitory activity at an $IC_{50}$ of less than 50 μM", out of Examples 1-1094, only 2 compounds have R7= CH3, the other compounds are not encompassed by formula (I), since R7=H in those compounds. There is no specific data i.e raf kinase inhibitory activity data, provided for any compounds of formula (I) wherein R7 is loweralkyl group. Further the assertion that the compounds exhibited raf kinase inhibitory activity at an $IC_{50}$ of less than 50 μM does not guide one as to what

compounds have activity and as the difference in activity of from 5 nM to 50 μM is more than a 1000 fold one would need to know the activity profile of the specific compounds tested in order to understand the scope and breadth of the invention.

There are no working examples for the method of inhibiting Raf kinase activity in a human or animal comprising administering any compounds of Formula (I) or ester or prodrug thereof.

**(5). State of the Art: / (6). Predictability of the Art:**

While the state of the art is relatively high with regard to a method of inhibiting Raf kinase activity in human or animal comprising administering specific compounds, the state of the art with regard to a method of inhibiting Raf kinase activity comprising administering any compounds encompassed by formula (I) is underdeveloped.

It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839 (1970). In the instant case, as discussed above, there is a vast number of compounds encompassed by the claims, the specification merely recites that the compounds of Examples 1-1094 were shown to have a raf kinase inhibitory activity at an $IC_{50}$ of less than 50 μM, out of Examples 1-1094, out of Examples 1-1094, only 2 compounds have R7= CH3, the other compounds are not encompassed by formula (I), since R7=H in those compounds. The compounds represented by formula (I) have different functional groups, and will have different properties, e.g., physical, chemical, physiological effects and functions, since given the fact that any significant structural variation to a compound

would be reasonably expected to alter its properties. Furthermore, there is no evidence that the compounds actually inhibit Raf kinase activity in a human or animal. For example, a compound with R7=CH3, Y=O, R1=O, R2=OH in formula (I) will have different properties such as binding abilities, solubilities, properties than a compound with R7 = neopentyl or pentafluoroethyl group, Y=S, R1, R2 form a heterocycloalkyl, and thus will have different raf kinase inhibitory activity. Furthermore, there is no evidence that the compounds actually inhibit Raf kinase activity in a human or animal. Moreover, one of skill in the art would recognize that it is highly unpredictable in regard to therapeutical effects, side effects, and especially serious toxicity that may be generated by drug-drug interactions when and/or after administering to a host (e.g., a human) any compound represented by formula I, and other anticancer agents. See "Goodman & Gilman's The Pharmacological Basis of Therapeutics" regarding possible drug-drug interactions (9th ed., 1996), page 51 in particular. Goodman & Gilman teaches that "The frequency of significant beneficial or adverse drug interactions is unknown" (see the bottom of the left column of page 51 ) and that "Recognition of beneficial effects and recognition of and prevention of adverse drug interactions require a thorouqh knowledge of the intended and possible effects of drugs that are prescribed" and that "The most important adverse drug-drug interactions occur with drugs that have serious toxicity and a low therapeutic index, such that relatively small changes in drug level can have significant adverse consequences" (see the right of page 51) (emphasis added). Thus, the compounds of formula (I) and their esters, prodrugs thereof of the instant invention have different functional groups and result in different biological

properties such as drug-drug interactions, formation of metabolites with different toxicities etc. Thus, the instant claimed invention as discussed above is **highly unpredictable**. The specification do not disclose which "compounds of formula (I) with R7=alkyl were tested, and do not disclose the specific Raf kinase inhibition activity of any of the compounds of formula (I).

Moreover, the standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court of Mineral Separation v. Hyde, 242 U.S. 262, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied.

**(7). The Quantity of Experimentation Necessary:**

In order to practice the claimed invention, one of skill in the art would have to first envision a compound, a dosage for each compound, an appropriate pharmaceutical carrier, the duration of treatment, route of treatment, etc. and, in the case of human treatment, an appropriate animal model system for one of the claimed compounds. One would then need to test the compound in the model system to determine whether or not the compound is effective for inhibiting Raf kinase acitivity, and determine whether or not the compound is effective in inhibiting Raf kinase acitivity in a human or animal subject suffering from a Ras/mitogen-activated protein kinase signal pathway-mediated cancer disorder selected from the group consisting of melanoma, breast cancer, prostate cancer, lung cancer, pancreatic cancer, thyroid cancer, bladder cancer, colon cancer, liver cancer, myeloid leukemia, and villous colon adenoma. One would then

also need to test the compound in the model system for side effects and toxicity at the site of pharmacological action and the therapeutic index of the drug. Thus a person of skill in the art would have to engage in **undue experimentation** to test these compounds encompassed in the instant claims and their combination with other drugs to be administered to a host employed in the claimed methods of the particular treatments herein, with no assurance of success. If unsuccessful, , one of skill in the art would have to then either envision a modification of the first pharmaceutical compound, compound dosage, duration of treatment, route of administration, etc. and appropriate animal model system, and test the system again. Therefore, it would require undue, unpredictable experimentation to practice the claimed invention to inhibit Raf kinase activity in a human or animal subject by administration a composition comprising one of the compounds represented by formulas (I) or ester or prodrug thereof.

Genetech, 108 F.3d at 1366 states that “a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, the instant specification, does not enable the skilled artisan to make and use the claimed invention commensurate in scope with these claims.

***Response to Applicant’s Arguments:***

Applicant's arguments with respect to claim rejections have been considered but are moot in view of the new ground(s) of rejection.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 75-76, 78, 80, 82-83, 87-106, 108-112 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation, "ester or pro-drug thereof", of compound of formula (I) in these claims render claims herein indefinite. The recitations, "ester or pro-drug thereof", of the compounds of formula (I) are not clearly defined in the specification. Hence, one of ordinary skill in the art could not ascertain and interpret the metes and bounds of the patent protection desired as to "ester or pro-drug thereof", of compounds of formula (I) herein, since one of ordinary skill in the art would clearly recognize that many widely varying groups could possibly substituting the compounds herein would read on the "ester or pro-drug thereof", of the compounds. For example, esters are obtained by reacting an acid group of the instant compound with any alcohol or by reacting an -OH group of instant compound with an any acid. Hence, one of ordinary skill in the art could not ascertain and interpret the metes and bounds as to "ester or pro-drug thereof", since one of ordinary skill in the art would clearly recognize many, various, and possibly esters obtained from wide variety of alcohols, and acids.

Given the fact that any significant structural variation to a compound would be reasonably expected to alter its properties, e.g., physical, chemical, physiological effects

and functions. Thus, it is unclear and indefinite as to the "pro-drug thereof" or "esters thereof of compounds herein encompassed thereby.

## *Conclusion*

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shobha Kantamneni whose telephone number is 571-272-2930. The examiner can normally be reached on Monday-Friday, 8am-4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, Ph.D can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Patent Examiner
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/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1617

| Application Number | Application/Control No. | Applicant(s)/Patent under Reexamination | |
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| | 10/675,927 | AMIRI ET AL. | |
| | Examiner | Art Unit | |
| | Shobha Kantamneni | 1617 | |